hepatitis A virus, NonA/NonB hepatitis virus, and flavivirus immunogens.

152 (amended). The kit of claim 16 in which at least one immunogen is

(a) an immunogen of an organism which causes a disease selected from the group consisting of measles, mumps, rubella, diphtheria, pertussis, tetanus, anthrax, plague, encephalitis, meningitis, pneumonia, typhus, typhoid fever, Lyme disease, cholera, leprosy, influenza, varicella, rabies, dengue, toxoplasmosis, coccidiomycosis, schistosomiasis, and malaria, or

(b) an immunogen selected from the group consisting of BCG, *Hemophilus influenza*, hepatitis B virus, polio virus, *Streptococcus, Staphylococcus, Neisseria, Escherichia coli, Shigella, Leishmania*, cytomegalovirus (CMV), respiratory syncytial virus, Epstein-Barr virus, herpes virus, parainfluenza virus, rotavirus, adenovirus, human immunodeficiency virus (HIV), hepatitis A virus, NonA/NonB hepatitis virus, and flavivirus immunogens.

REMARKS

1. Election/Restriction (OA§2)

Unelected claims have been cancelled without prejudice or disclaimer.

2. Objections (OA §4)

Claims 5, 30, 56, 67, 71, 73, 144, 149, 150 and 152 have been amended to satisfy the examiner's concerns.

3. Definiteness Issues (OA §§5-6)

3.1. The rejection is applied to claims 5, 6, 8-11, 16, 27-30, 34-47, 49-57, 77 and 86 for reasons of record". However, the only response made to Applicant's arguments was with respect to claims 6, 57 and 40, and in the case of 6 and 57, it merely

reiterated the Examiner's conclusion. The rejection is therefore procedurally defective.

3.2. The Examiner previously questioned the antecedent basis for the "after birth" limitations in claims 6, 57, 11 and 38:

> Claim 6 is indefinite as lacking clear antecedent basis. Claim 6 recites "wherein for at least one such immunogen, the total dosage during the first 112 days after birth...". Claims 6 depends from claim 32, which recites dosages during the first month or prior to 42 days after birth, not 112 days. Claim 57 is also indefinite for the same reason; claim 57 depends from claim 56, which also recites dosages during the first month or prior to 42 days after birth.

The Examiner has never clarified the reason she considers "first 112 days after birth" to lack antecedent basis.

If it is that we did not recite, in the main claim, "said subject having a date of birth," then we must respectfully traverse.

MPEP §2173.05(e) says that "the failure to provide an explicit antecedent basis for terms does not always render a claim indefinite. If the scope of a claim would be reasonably ascertainable by those skilled in the art, then the claim is not indefinite.... Inherent components of elements recited have antecedent basis in the recitation of the components themselves". The date of birth of a person is inherent to that person.

Similar language was permitted in prior patents of this family, USP 5,723,283 (cp. claims 12 and 13) and USP 5,728,385 (cp., e.g., claims 1, 7 and 9).

If the Examiner's concern is with the differency in the periods, i.e., the Examiner simply thought that there was an inconsistency between reciting the "first 112 days after birth" in claim 6 and "prior to 42 days after birth" in base claim 32. If so, we can readily resolve the issue.

Claim 32 requires that for at least one immunogen, the first dose of the immunization schedule be administered when the mammal was "less than 42 days old, measured from both".

Claim 6 required that for at least one immunogen, the total dose administered under the schedule during the first 112 days after birth be substantially greater than that required for immunization against the corresponding infectious disease.

This language is readily harmonized. On page 32, Applicant presents several conventional immunization schedules, with DTP given at weeks 6, 10 and 14. Thus, there are 3 DTP doses in the first 112 days (16 weeks) after birth, and this is presumably all that is required for immunization against these diseases. On page 107, several preferred immunization schedules are given. In schedule 1, the first DTP dose is given in week 0, so the "first dose less than 42 days after birth" requirement of claim 32 is plainly satisfied. DTP is given in weeks 0, 2, 4, 6, 8, 10, 12 and 14, a total of 8 doses in the first 112 days after birth. Even if we ignored the last dose, the total dose plainly exceeds that required for protection against diphtheria, tetanus and pertussis, see page 32, and hence satisfies claim 6.

Similar arguments may be made concerning claims 11, 38 and 57.

3.3. We have deleted "substantially" from claim 40.

3.4. The Examiner has not formally responded to our explanation that all members of the questioned markush groups (presumably, those of claims 5, 30, 37, 56 and 77) are immunogens, but that some are identified by their source organism directly, and others by the diseases with which they are associated (and hence may embrace immunogens from more than one organism). The wording of the objection suggests that this reasoning is accepted by the Examiner, so we do not understand why the rejection is maintained.

3.5. Reviewing the file, we were unable to identify in the

file any specific explanation of why claims 8, 10, 11, 16, 27-29, 34-36, 38-46, 49-55 and 86 have been rejected. They do not recite "days after birth", "substantially", or a markush group, and they are not (like 57) dependent on any claim which does.

3.6. As a new ground of rejection (OA §6, p. 5) the Examiner asserts:

> Claims 5, 30, 32, 67, 71, 73, 77-85, 144, 149, 150, 151, and 152 recite "an immunogen of an organism" which causes one of a group of specifically recited diseases. The specification fails to teach what organisms are the etiologic agents of the recited diseases and fails to teach what is encompassed within an immunogen of the organism. Absent such disclosure, the metes and bounds of the claimed invention cannot be ascertained and the claims are indefinite.

We are not aware of any authority which requires that an immunogen be identified by source organism rather than by disease.

3.7. Claims 144, 145 and 147 recite "substantially".

The use of the relative term "substantially" has been repeatedly upheld when a suitable standard, such as a stated purpose, or representative examples, are disclosed. Andrew Corp. v. Gabriel Electronics, Inc., 6 USPQ2d 2010, 2012 (Fed, Cir. 1988); Seattle Box Co., Inc. v. Industrial Crafting & Packaging, Inc., 221 USPQ 568 (Fed. Cir. 1985); In re Mattison, 184 USPQ 485 (CCPA 1975).

The Examiner says that no standard is provided. We disagree.

First of all, page 55, lines 17-20 refers to a reduction in incidence of 50%-75%.

In Ex. 1, the incidence of diabetes was reduced from 65% at 28 weeks in NOD mice, to 57.9% for the plague vaccine group and 42.1% for the anthrax vaccine group. See page 82, lines 21-27.

That is a reduction of 7.1 percentage points out of 65, or 10.9%, for the plague vaccine, and 22.9 percentage points out of 65, or 35.2%, for the anthrax vaccine.

In Ex. 4, an experiment was conducted with another diabetes model, BB rats. The rats given anthrax + DTP had a diabetes incidence of 35% at 32 weeks, as compared to 54% for control rats. This was, as noted in the spec., a 34% reduction in incidence. See page 87, lines 15-22.

Other reductions in incidence may be extracted from the other examples, experimental and epidemiological, but the above seems sufficient to establish a standard.

3.8. Claim 146 requires a total dosage during the first 112 days after birth which is greater than that required for immunization against the infectious disease with which it is associated. The Examiner complains that the "specification fails to teach what diseases are associated with immunogens, fails to teach the metes and bounds of the dosage required for immunization against an associated disease, and fails to teach what is encompassed within a greater total dosage".

There are, of course, many disease for which associated immunogens are already known. For other diseases, the associated immunogens can be determined in the already conventional ways.

The present invention does not claim a method of determining the immunogens (or organisms) associated with a disease. Rather, once it is determined that an immunogen is so associated, and is protective, it explains how to administer the immunogen while minimizing the risk of developing a chronic immune-mediated disorder.

3.9. The examiner questions whether the state of maturation of the immune system (claim 148) is known in the art, or determinable without undue experimentation, for mammals other than mice or rats, or how it is to be correlated to that in a mouse or rat.

This claim is based on page 29, lines 13-19 of the specification:

> The present invention therefore can include administration of the immunogens to humans when said humans immune systems are in a state of maturation and responsiveness comparable to that of mice or rats at the times indicated above, in such circumstances as it would be less effective to administer those immunogens to humans at the same chronological ages as they were administered to mice or rats.

The Examiner says that no markers of maturation are disclosed. This ignores the text at page 27, line 15 to page 29, line 12.

At page 27, lines 15-23, we begin:

> The immune systems of mice and men mature at comparable rates, with both species capable of mounting immune responses to vaccine antigens by the time the recipients are several months old. A comparison of the experimental and epidemiological examples in this specification supports this conclusion. Subtle differences in the rates of development of the immune systems of mice and humans may be detected however using a broad range of assays including <u>in vivo</u> assays, <u>in vitro</u> assays, <u>in vitro</u> assays and phenotypci cell assays.

The markers subsequently disclosed include:

(1) antibody titers in blood;

(2) DTH response;

(3) ability of T-cells to divide;

(4) ability of B-cells to divide;

(5) ability of immunocytes to secrete specific lymphokines;

(6) number of lymphocytes in the blood; and

(7) number of macrophages in the blood.

We do not understand why "correlation" should present any

difficulties.

3.10. We have amended claim 148 to specify that the maximum interval is at least one day. The reasoning is the same as it was for claim 40.

3.11. The term "flavivirus antigens" (149-152) has the self-evident meaning of antigens of the flaviviruses. The specification need not disclose specific viruses or antigens. The flaviviruses are a known viral class.

3.12. There is no legal basis for objecting to recitation of a markush group as a member of another markush group. If the Examiner is aware of such authority, he should cite it.

However, in claims 150-152, we have now "or-ed" (a) and (b), instead of using Markush language. This just not affect claim scope.

3.13. Claims 156, 157 and 160 were intended to depend from claim 153. Since claim 153 was restricted out, we cancelled 156, 157 and 160.

4. Description/New Matter Issues (OA §§7-8)

4.1. The rejection here repeated was first made on June 20, 2000, pp. 5-7. That rejection only discussed claims 32, 56, 58, 59 and 89. Claim 58 was cancelled, and claims 32, 59 and 89 defended on pp. 15-16 of our December 19, 2000 amendment. Claims 32 and 59 were defended once again on pp. 19-32 of our August 17, 2001 amendment, while claim 89 was cancelled.

It does not seem to us that the Examiner's one paragraph dismissal of our arguments as previously addressed can possibly be considered responsive. We incorporate by reference our prior remarks.

4.2. We set forth the basis for claims 144-148 at pp. 10-11 of the August 17 amendment. The Examiner has specifically questioned some of the language of claims 40 and 145-148, which we defend as follows:

40 ("at least one"): See page 26, lines 8-11.
145 ("four different dates"): See page 26, line 5.
146 (total dosage in first 112 days): See original claim 6.
147 (not pertussis, and at least 3 doses): See original claim 5, line 2, and page 26, line 4.
148 ("the first dose...mouse or a rat"): See page 27, line 15 to page 29, line 19.
149 (limitations (a) and (b)): See prior discussion of claim 32.

5. Enablement Issues (OA §§9-10)

5.1. Referring first to page 8, second full paragraph, of the action, the Examiner acknowledges that claims 102, 104, 105 and 107-127 are not rejected for lack of enablement. However, the rejection is still applied to 131-136, which are dependent on 127 (see top of page 24 of our August 17 amendment), and thus is still inconsistent.

5.2. With regard to the rejected claims, the Examiner only deigns to specifically address the Classen & Classen (C&C) citation. The examiner says that this reference teaches away from enablement of the present claims, "as it teaches a correlation between an increased risk of IDDM (a chronic immune-mediated disorder) and immunization".

Plainly, the Examiner misunderstands the disclosure and claims. Applicant did not teach that all immunization protects against CIMD, or that all immunization increases CIMD. Rather, Classen's application taught that immunization can affect CIMD, and that the direction of the effect is timing dependent. This is reflected in the claims.

5.3. The Examiner says that the rejection is formally for lack of enablement, rather than for lack of utility. With regard to enablement vs. utility (OA page 8, lines 6-9), in our view,

when the Examiner questions the believability of a utility, she is making a utility rejection, while when the Examiner questions the quality of the written disclosure of a believable utility, she is making an enablement rejection. See MPEP 2164.07. Here, the examiner questions extrapolation of animal data, which is a typical utility issue, see MPEP 2107.02 (III). In other words, this is a utility rejection in "enablement rejection clothing", and the utility guidelines should apply. Hence, procedurally, these utility issues should be raised in a combined 101/112 ¶1 rejection, and any pure enablement issues in a separate 112 ¶1 rejection, see MPEP 2164.07. The Examiner has plainly questioned the utility of the claimed method in humans. We have claims that are limited to humans.

5.4. Applicants previously pointed out that the utility/enablement of this claimed invention is supported by human epidemiological data, see Appeal Brief pp. 28-29, 36, 41-43; August 17, 2001 Amend at 25. The Examiner continues to dismiss Applicant's epidemiological data as irrelevant. While some may argue that it does not prove the causal relationship, it nonetheless renders the proposed utility believable. The Examiner has failed to answer this point. In In re Irons, 144 USPQ 351 (CCPA 1965), the court accepted historical data as evidence of utility.

If, by the way, applicant's epidemiological data is irrelevant, then is the examiner still relying on the epidemiological data of the Halsey PIDJ article? What is sauce for the goose should be sauce for the gander. If the Examiner still relies on PIDJ, then Applicant in turn relies on pp. 16-26 of the December 19, 2000 amendment.

5.5. The Examiner likewise has failed to respond our arguments concerning the animal data in examples 1-5, and the propriety of extrapolating from that data to humans. See, in particular, pp. 25-26 of the August 17, 2001 response, and pp.

27-28 and 38-41 of the Appeal Brief. If enablement for additional immunogens is still questioned, as intimated by OA §6, we direct the Examiner to pp. 30-36 of the Appeal Brief.

5.6. OA §10 raises issues concerning certain newly added claims that we have, more or less, seen before. These include questions concerning (1) identification of immunogens for a specific organism (e.g., flavivirus) or disease, or contrariwise, or the disease associated with a particular immunogen, (2) determination of the dosage for protection against the CIMD, and (3) determination of the dosage for protection against the ID.

For point (3), see pp. 47-49 of our Appeal Brief. For point (2) see pp. 52-55 of our appeal brief. As for point (1), the bottom line is that the present invention does not relate to finding an immunogen to protect against an infectious disease, but rather to making sure that, in carrying that vaccination against an infectious disease, one does not inadvertently increase the risk of a CIMD. As new immunogens or infectious diseases are recognized, applicant's methods can be applied to them with an expectation of success, see pp. 30-34 of the Appeal brief.

5.7. Claims 102, 104, 105 and 107-127 were not rejected for lack of enablement and we hope that the examiner will suggest amendments that would overcome the remaining rejections of these claims.

6. Double Patenting (OA §11)

It is requested that this rejection be held in abeyance until all pending claims are held allowable save for this rejection.

7. Anticipation (OA §12)

7.1. The rejections over Madore and (in part) John were withdrawn.

7.2. Rejections over Halsey, John and Benveniste were maintained. New claims 149-152 have been rejected over Madore, Dengrove, Halsey and Benveniste, and 151-152 over John as well.

The labeling is what the PTO calls "printed matter". Printed matter may constitute an element of a patentable claim and be given patentable weight, if there is a sufficient functional relationship between the printed matter and its substrate. See In re Gulack, 217 USPQ 401 (Fed. Cir. 1983); In re Miller, 164 USPQ 46 (CCPA 1969). Here, the printed matter explains how to use the substrate (the immunogen) to achieve the desired result (reduction in the incidence or severity of a chronic immune-mediated disorder).[1]

While, in a claim to a product, language of intended use is ignored, these kit claims require the presence of certain labeling. This is a tangible requirement, not a mere statement of intended use.

What is a "functional relationship"? Presumably, it implies that without the printed matter, the substrate would be **less capable** of performing its function.

In the case of In re Miller, claim 10 read as follows:

> A measuring device comprising: a spoon for measuring ingredients; and volume measuring indicia defined in a normal volumetric unit on said spoon of a selected ratio to but indicating a volume different from the actual volume of ingredients being added to and measured in said spoon by said indicia,

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[1] The "printed matter" doctrine is closely allied with the old "mental steps" and later "mathematical algorithm" doctrines, and, in this regard, it is interesting to note that an invention applying the rules and instructions for a game ("Cricket") to an otherwise old dart machine was held to be potentially patentable because the algorithm was not a mathematical one. See Arachnid Inc. v. Medalist Mktg. Corp., 18 USPQ2d 1941 (W.D. Wash. 1991). The claimed instructions for use do not define a mathematical algorithm.

and a legend attached to said spoon specifying said ratio.

The court's opinion reproduces two apparatus of this type. In Fig. 2, we see a measuring cup with the legend "ONE HALF RECIPE", and various volumetric indicia. The line marked "2 CUPS" actually corresponds to a volume of one cup, so, if a full recipe called for "2 cups", by filling to the line in question, one would actually be adding the amount appropriate for a half recipe. In Fig. 3, we see a set of measuring spoons with a "½ recipe" tag. Here, the spoon marked "1 teaspoon" has a true capacity of ½ teaspoon.

Were these indicia and legends to be removed, one would have cups and spoons worthless for accurate measurement. If just the legends were removed, one would have just a conventional looking (but inaccurate) measuring device or cup. The Court found that there was "a new and unobvious functional relationship between a measuring receptacle, volumetric indicia thereon indicating volume in a certain ratio to actual volume, and a legend indicating the ratio".

Similarly, in the instant kit claims, there is a new and unobvious relationship among "containers holding pharmaceutically acceptable doses of one or more immunogens" (which is like Miller's "receptacle") the "labeling" of the containers to indicate the identity and amount of each immunogen they contain (which is like Miller's "volumetric indicia")[2] and the "instructions" for use (which is like Miller's "legend").

The last of these points deserves particular emphasis. Miller's "legend" is an instruction for use. "One Half Recipe" is an instruction to the cook to use the cup or spoon se tin question when he or she wishes to prepare a "one half" recipe

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[2] While this is not explicit in claims 27 and 29, it is an FDA requirement. The Supplemental Amendment, if entered, would make this explicit.

without recomputation of the required amount of each ingredient. Without the cook to interpret the legends and indicia, the cup and spoons do not perform any function. Their functionality resides in what they communicate to the cook. They do not help the receptacle hold more ingredients, or keep them fresher. They do not make the receptacle more watertight or airtight. Their relationship -- especially the legend's relationship -- to the receptacle is closely akin to the relationship exhibited by the printed matter in the instant kit claims to the immunogens of those claims.

In Gulack, the claim was to an educational device, which could take the form of a hat with a headband. Imprinted on the headband (the substrate) was a cyclic sequence of integers (the printed matter) obeying a particular mathematical rule. What was the functional relationship? According to the CCPA, the digits -- the printed matter -- were "related to the band in two ways: (1) the band supports the digits; and (2) there is an endless sequence of digits... exploit[ing] the endless nature of the band". In contrast, in the prior art Wittcoff reference, there was printed matter on the band, as in (1) above, but the data items were independent rather than arranged in a particular sequence.

Here, the labeling establishes a sequence, albeit temporal rather than spatial, for the use of the immunogens of the kit. Bear in mind that this relationship is between the printed matter and the immunogens, which are a part of the overall "substrate". In Gulack, the distinguishing relationship was between one printed element and another printed element. Hence, the present case actually presents a stronger justification for the finding of a functional relationship than does Gulack.

While the immunogens are functional despite the labeling, that does not mean that a functional relationship is absent. Congress, in enacting the Food, Drug and Cosmetic Act (FDCA),

recognized the existence of a functional relationship between a drug and its labeling. Thus, a new drug is not approved per se, rather it is approved for a particular indication (use). The new drug application includes "specimens of the labeling proposed to be used for such drug", see FDCA Sec. 505(b)1)(F). The FDA reviews the NDA and can refuse to approve if the testing was inadequate to show that "such drug is safe for use under the conditions prescribed, recommended or suggested in the proposed labeling thereof" (see FDCA Sec. 505(d)(1)) or the results "show that such drug is unsafe for use" or "do not show that such drug is safe for use" under "such conditions" (see FDCA Sec. 505(d)(2)). Moreover, approval may be refused if "such labeling is false or misleading in any particular" (see FDCA Sec. 505(d)(7)).

Once a new drug has been approved, that approval may be withdrawn for the same reasons that approval could have been withheld in the first place. See FDCA Sec. 505(e).

Moreover, the FDCA draws a distinction, for all drugs, between adulteration and misbranding. If a drug contains a substance which is deleterious to health, it is adulterated. See FDCA Sec. 501. However, even a drug free of deleterious substances can be sanctioned if it is misbranded. A drug is misbranded if "its labeling is false and misleading in any particular", see FDCA Sec. 502(a). More significantly, it is misbranded "unless its labeling bears (1) adequate directions for use; and (2) such adequate warning against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application." See FDCA Sec. 502(f). A possible loophole is closed by FDCA Sec. 502(j), which says that a drug is "misbranded" if it is "dangerous to health when used in the dosage manner, or with the frequency or duration prescribed, recommended or suggested in the labeling thereof."

Prescription drugs dispensed by filling the prescription of a physician are exempt from Sec 505(f) and (j), cited above, but only if the drug bears a label presenting "the directions for use and cautionary statement, if any, contained in such prescription." FDCA Sec. 503(b)(2)

According to 21 CFR §201.57(e),

> Under this section heading, the labeling shall describe serious adverse reactions and **potential safety hazards, limitation in use imposed by them,** and steps that should be taken if they occur. **The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved**.

Plainly, FDA realizes that some manufacturers and this consultants will argue their product has not been proven to cause a serious adverse event even though the data shows an association. FDA requires manufacturers to warn about a potential adverse event as soon as there is any reasonable evidence of an association. This is because it feels that the cost to the public of an unnecessary warning is much less than that of a delayed one.

While a physician may prescribe a drug for an off-label use without violating the FDCA, such prescription may be considered medical malpractice, and insurers may refuse to pay for such use.

We caution the Examiner against an overly restrictive definition of a "functional relationship", namely, that "without the printed indicia or numbers, the substrates lose their function." The case law does not justify that definition.

In Gulack the substrate was a headband. It remained functional as a headband, only its educational function would have been lost if the integer sequence were omitted. In Miller, the substrate was a measuring cup or spoon. It could still be

used as a cup or spoon if the indicia were omitted. Thus, it is clear that neither case presented a substrate whose function was totally dependent on the indicia.

Here, it is true that the immunogen (if protective in its own right) could be used to protect against the corresponding infectious disease. However, without the claimed directions for use, the clinician would not know how to use it to limit the increased incidence or severity of the disorder attributable to late immunization.

In determining the functionality of an immunogen, it is appropriate to consider its side effects, not just its specific immunogen effect. If the side effects are detrimental, its functionality is reduced. If the side effects are beneficial, its functionality is enhanced.

The fact the immunogen has a residual level of functionality, absent the indicia, does not mean that there is no functional relationship between the immunogen and the indicia (labeling). If the latter increases the functionality of the immunogen, the necessary relationship exists and it is proper to give patentable weight to the labeling limitation.

An interpretation of "functional relationship" as meaning necessary for the functioning of the substrate is inconsistent with the alternative holding of the Federal Circuit in In re Lowry, 32 USPQ 2d 1031 (Fed. Cir. 1994). Lowry claimed memory for storing data which comprised a particular data structure (a pyramidal and hierarchical arrangement of "attribute data objects", ADOs), a data processing system comprising a database, a CPU, and memory means for holding the claimed data structure and methods of manipulating ADOs. The Examiner rejected the memory claim under ' 101, the system claims as obvious, and the method claims as anticipated. The Board reversed the ' 101 rejection, and upheld the prior art rejections. According to the Board, Lowry's data structures were analogous to "printed matter"

and lacked a "functional relationship" to the substrate (the memory).

On appeal, the Federal Circuit held that because Lowry's data structures upon storage in memory, cause electromagnetic changes, there is a physical change, albeit invisible to the eye, and hence the data structures are not analogous to "printed matter".

However, it continued that even assuming that the analogy is valid, the Board erred in its reliance on Gulack. It pointed out that the ADOs enabled "more efficient data processing operations on stored data" in particular, that they "facilitate addition, deletion and modification of information stored in memory". The memory, of course, has a "function" even without Lowry's data structure. Lowry's merely structures "provided increased efficiency". However, that qualified as a "functional relationship": "In sum, the ADOs perform a function, Gulack requires no more".

We also think it worth reiterating that if the labeling is given patentable weight (as we think proper as a matter of law), it is clear that the claims are not anticipated or rendered obvious by the reference. While it is certainly normal for an immunogen to be labeled with directions for use, to immunize against an infectious disease, and with warnings of side effects like acute toxicity, applicant was the first to teach that it should be labeled to direct its administration so as to limit the increased incidence and severity of a chronic immune mediated disorder (e.g. diabetes).

Consistent with this analysis, the PTO has allowed claims with "labeling" limitations.

Gerbe, USP 3,627,122, SYSTEM AND APPARATUS FOR THE ADMINISTRATION OF DRUGS (1971), claims an apparatus comprising compartmented trays, with "a patient and dose identification card" covering the bottom of each compartment, the card "having

a folded portion...for holding said card in place". The claim also recites that each compartment has "a longitudinal pocket in one wall for a signal identification card".

Phykitt, USP 5,687,841, COMBINATION SHIPPING CONTAINER, MIXING AND DRINKING VESSEL (1997) claims the combination of analgesic medications and a package which serves both a shipping container and a mixing vessel. Claims 21-22 recite

> 21. The combination, according to claim 1, wherein said package further includes at least one of indications, directions, warnings, drug interaction precautions, active ingredients information and storage information disposed on an outer surface of one of said back portion and said front portion of said package.
>
> 22. The combination, according to claim 21, wherein said package includes each of said indications, said directions, said warnings, said drug interaction precautions, said active ingredients information and said storage information disposed on said outer portion of said back portion of said package.

Robertson, USP 5,752,723, PHARMACY LABEL AND PRESCRIPTION DRUG DISPENSING (1988) claims (18) "a labeled prescription drug package comprising...indicia comprising the name of a prescription drug, the dosage for proper administration of the drug, and the quantity of the drug to be provided in a package, imaged on said first label section".

See also Olney, USP 5,011,853 (claim 18= "a label which indicates that said pharmaceutical agent can be used for reducing the neurotoxicity of at least one cholinergic neurotoxin"); Kelly, USP 5,208,031 (claim 4= "the packaging material indicates that the sexual lubricant mixture... can reduce the risk of being infected by at least one type of sexually transmitted virus"); Sanders USP 4,820,635 (claim 1= "A kit ...comprising... instructions for performing the assay").

This is the first of several points in the brief in which we cite prior patents as evidence that a particular claim is acceptable. while we agree with the PTO that such evidence is not conclusive -- it certainly could not justify a legal position which was plainly contrary to the patent statute -- we cannot agree that is legally irrelevant. The courts have repeatedly found such evidence to be probative. Of course, the greater the number of patents cited, the more weight they carry. And the examiner is welcome to attempt to rebut the evidence of showing that a difference in the disclosure justified the difference in prosecution. However, the examiner cannot simply ignore the evidence.

The following cases illustrate the relevance of prior patents:

> Ex parte Brian, 118 USPQ 242, 245, (POBA 1958) (past practice of office in accepting definiteness of "fingerprint" claims);
>
> In re Chakrabary, 596 F.2d 952, 985-86 (CCPA 1979) (product claims reciting microorganisms previously treated as directed to statutory subject matter);
>
> Andrew Corp. v. Gabriel Electronics, Inc., 6 USPQ 2010, 2012 (Fed. Cir. 1988) (term "substantially" is "ubiquitous" in patent claims and therefore considered definite);
>
> In re Cortright, 49 USPQ2d 1464 (Fed. Cir. 1999) (Construction of "restore hair growth" for purpose of determining both §112 enablement and §101 utility; prior art references may be indicative of how a claim term will be interpreted by those of ordinary skill in the art);
>
> Vitronics Corp. v. Conceptronic Inc., 39 USPQ2d 1573, 1578-9 (Fed. Cir. 1996) (prior art used to demonstrate how a disputed term is used by those skilled in the

art, and indeed is more objective and reliable than post-litigation expert opinion testimony); Pioneer Hi-Bred International v. J.E.M. Ag Supply Inc., 49 USPQ2d 1813, 1819 (N.D. Iowa 1998) (issuance of Boehm USP 2,048,056 in 1936 is evidence that "in those instances where inventors showed they could define a reproducible plant meeting the limits of §112, plant patents were issued under §101".)

The purpose of the patent system is to encourage innovation. The claims are a means of defining the invention in such a manner that it is reasonably clear what has been patented. It is one thing to reject a claim because it covers subject matter which is disclosed or suggested by the prior art, or which is not enabled. It is quite another to reject it on what amounts to stylistic grounds.

The PTO and the courts have recognized the propriety of once exotic claim formats-- "Jepson" claims, "Markush" claims, "product-by-process" claims, "fingerprint" claims, and claims with "negative", "functional", or "alternative' limitations -- because they have realized that public policy demands that inventors not be hindered by hypertechnical claim drafting rules from fully protecting novel, nonobvious, and adequately disclosed inventions.

The instant "kit" claims are a case in point. Applicant has discovered that immunization can --depending on timing - either increase or decrease the incidence or severity of chronic immune-mediated disorders such as diabetes and SLE. A traditional product claim does not sufficiently protect applicant, as it cannot cover a prior art vaccine, even if that vaccine were used without consideration of its effect on a chronic immune-mediated disorder.

For a method claim to protect the invention, it must be crafted to avoid any instance in which the prior art use of a

vaccine to immunize against an infectious disease might inherently (although inadvertently) have had the effect of also reducing the incidence or severity of a chronic immune-mediated disorder, as otherwise it could be held invalid on the ground of "inherent anticipation". Applicant has studied the literature, and has attempted to phrase the claim so as to avoid inherent anticipation, but simply cannot be sure that all such art has been avoided. An early immunization protocol might be set forth in an old or obscure journal anywhere in the world, or might have been used "publicly", without formal publication, in the United States. Indeed, the specification at page 31, lines 9-18 expressly recognizes the problem:

> The inventor appreciates that it is conceivable that a prior experimenter has, without recognition of its anti-chronic immune-mediated disorder activity, proposed or even practiced an immunization schedule which falls within the present disclosure, If, under the applicable law, such a proposal or practice would be deemed to anticipate or render obvious an invention here claimed, then it is within the inventor's contemplation to excise from the invention the specific embodiment in question, preserving to the maximum degree permitted by law the scope of protection originally sought.

A second problem with method claim protection is that it is geared to use of immunogens to decrease the incidence or severity of a chronic immune-mediated disorder. However, the Applicant has also enriched the art by teaching it to examine the chronic immune effects of conventional immunization. A vaccine manufacturer may find, after testing inspired by Applicant, that early immunization, while less likely to elicit this adverse effect, is also less effective against the infectious disease, and therefore continue to recommend, with appropriate warnings, late immunization. A "method of reducing the incidence or severity of a chronic immune-mediated disorder" claim would not reach this practice, even though the manufacturer would clearly have benefitted from Applicants's teachings.

A third problem is that the method claims are infringed by physicians. Applicant would prefer to assert direct infringement by the manufacturer. It is easier for Applicant to monitor vaccine labeling than to identify which doctors are following the claimed early immunization strategies.

A "kit" claim, like claims 27 and 59, solve these problems, without giving Applicant control of subject matter to which he is not entitled. Claim 27 and 59 are infringed only if the immunogen is distributed or sold with labeling either giving instructions which call upon the physician to practice the invention, or warnings indicating that the manufacturer has screened the immunogen as taught by Applicant.

Claims 27 and 59 could not be inherently anticipated by the naive use of the immunogen in an early immunization schedule, since such use, by definition, would make no reference to the effect of the immunogen on the incidence or severity of a chronic immune-mediated disorder.

Thus, we have explained why the functionality of the immunogens here should be deemed to be affected by the labelling, per Miller and Gulack. As for In re Giolito (1976), this hardly overrules the numerous post-1976 cases which have given weight to prior patents, see above.

7.3. In section 6.3 of our last amendment, we explained why this rejection is not properly applied to the method claims (e.g., 6, 32 and 33). The Examiner appears to have overlooked this analysis.

7.4. Claims 101, 103, 106, 128, 129 and 130-148 have not been rejected over prior art. We hope that the Examiner will suggest amendments to these claims that will resolve the non-art rejections.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "Version with markings to show changes made".

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

Claims 19, 153-258, and 260-265 have been cancelled.

Claims 5, 30, 56, 71, 73, 144, 148, 149, 150, 151, and 152 have been amended as follows:

5 (twice amended). The kit of claim 59 wherein one immunogen is provided which is not any of the following immunogens: a BCG, *Hemophilus influenzae, Streptococcus pneumoniae,* hepatitis A, hepatitis B, or *Neisseria* immunogen, or an immunogen of an organism which causes diphtheria, tetanus, pertussis, polio, [hepatitis A, hepatitis B,] measles, mumps , rubella, influenza, cholera, plague, varicella, rabies, typhoid or yellow fever.

30 (twice amended). The kit of claim 16 wherein said kit contains at least one immunogen selected from the group consisting of a *Hemophilus influenzae* immunogen, a BCG immunogen, a hepatitis B immunogen, and an immunogen of an organism which causes a disease selected from the group consisting of diphtheria, tetanus, polio, [Hepatitis B,] and pertussis.

56 (twice amended). A method of reducing the incidence or severity of an immune disorder in a mammal which comprises administering to said mammal one or more immunogens, according to an immunization schedule by virtue of which the mammal receives, at, one or more pharmaceutically acceptable doses of said immunogens, said administrations resulting in an immune response in said mammal which substantially reduces the incidence or severity of at least one chronic immune-mediated disorder in the mammal,

the first dose of said immunization schedule being administered when the mammal is less than 42 days old, measured from birth,

where, if only one immunogen is administered according to said immunization schedule, that immunogen is one other than BCG,

where, when all of the immunogens administered are selected from the group consisting of a BCG immunogen, a *Hemophilus influenzae* immunogen, a hepatitis B immunogen, and an immunogen of an organism which causes a disease selected from the group consisting of diphtheria, tetanus, pertussis, polio, [hepatitis B,] measles, mumps and rubella, at least one of the following conditions applies: (a) one or more immunogens are administered on at least three different dates prior to 42 days after birth, or (b) one or more immunogens are administered on at least three different dates, and the maximum interval between administrations is about two weeks, or less, and
where one or more immunogens are administered on at least four different dates.

67 (twice amended). The kit of claim 66 where said pediatric immunogen is selected from the group consisting of a BCG, immunogen, a *Hemophilus influenzae* immunogen, a hepatitis B immunogen, and an immunogen which causes a disease selected from the group consisting of measles, mumps, rubella, diphtheria, pertussis, [hemophilus influenza,] tetanus, [hepatitis B,] and polio.

71 (twice amended). The kit of claim 43 in which at least one immunogen is selected from the group consisting of a BCG immunogen, a *Hemophilus influenzae* immunogen, a hepatitis B immunogen, and an immunogen of an organism which causes a disease selected from the group consisting of anthrax, plague, tetanus, pertussis, diphtheria, [BCG,] hemophilus influenza and smallpox.

73 (twice amended). The kit of claim 72 where said pediatric immunogen is selected from the group consisting of a BCG immunogen, a *Hemophilus influenzae* immunogen, a hepatitis B immunogen, and an immunogen which causes a disease selected from the group consisting of measles, mumps, rubella, diphtheria, pertussis, tetanus, [hepatitis B,] and polio.

144 (amended). A method of reducing the incidence or

severity of a chronic immune-mediated disorder in a mammal which comprises administering to said mammal one or more immunogens, according to an immunization schedule by virtue of which the mammal receives, at, one or more pharmaceutically acceptable doses of said immunogens, said administrations resulting in an immune response in said mammal which substantially reduces the incidence or severity of at least one chronic immune-mediated disorder in the mammal,

the first dose of said immunization schedule being administered when the mammal is less than 42 days old, measured from birth,

wherein at least one immunogen is provided which is not any of the following immunogens: a BCG, a hepatitis A, a hepatitis B, a *Hemophilus influenzae, Streptococcus pneumoniae* or *Neisseria* immunogen, or an immunogen of an organism which causes diphtheria, tetanus, pertussis, polio, [hepatitis A, hepatitis B,] measles, mumps, rubella, influenza, cholera, plague, varicella, rabies, typhoid or yellow fever.

148 (amended). A method of reducing the incidence or severity of a chronic immune-mediated disorder in a mammal which comprises administering to said mammal one or more immunogens, according to an immunization schedule by virtue of which the mammal receives, at one or more pharmaceutically acceptable doses of said immunogens, said administrations resulting in an immune response in said mammal which substantially reduces the incidence or severity of at least one chronic immune-mediated disorder in the mammal,

the first dose of said immunization schedule being administered before the mammal's immune system arrives at a state of maturation comparable to that achieved at an age of 42 days after birth in a mouse or rat,

where, if only one immunogen is administered according to said immunization schedule, that immunogen is one other than BCG,

and, if said one immunogen is whole cell pertussis, the schedule is one other than a schedule of three doses at one week intervals, all given in the first month,

where, when all of the immunogens administered are selected from the group consisting of BCG, diphtheria, tetanus, whole cell pertussis, polio, hepatitis B, hemophilus influenza, measles, mumps and rubella immunogens, at least one of the following conditions applies: (a) one or more immunogens are administered on at least three different dates prior to 42 days after birth, or (b) one or more immunogens are administered on at least three different dates, and the maximum interval between administrations is <u>at least one day and not more than</u> about two weeks[, or less].

149 (amended). The kit of claim 68 in which said nonpediatric immunogen is selected from the group consisting of

(a) an immunogen of an organism which causes a disease selected from the group consisting of anthrax, plague, encephalitis, meningitis, typhus, typhoid fever, Lyme disease, cholera, leprosy, varicella, dengue, influenza, [herpes,] rabies, toxoplasmosis, coccidiomycosis, schistosomiasis and malaria, and

(b) an immunogen selected from the group consisting of *Streptococcus, Staphylococcus, Neisseria, Escherichia coli, Shigella, Leishmania,* cytomegalovirus (CMV), respiratory syncytial virus, Epstein-Barr virus, herpes virus, parainfluenza virus, rotavirus, adenovirus, human immunodeficiency virus (HIV), hepatitis A virus, NonA NonB hepatitis virus, <u>herpesvirus</u> and flavivirus immunogens.

150 (amended). The kit of claim 74 in which said nonpediatric immunogen is [selected from the group consisting of]

(a) an immunogen of an organism which causes a disease selected from the group consisting of anthrax, plague, encephalitis, meningitis, typhus, typhoid fever, Lyme disease, cholera, leprosy, varicella, dengue, influenza, herpes, rabies, toxoplasmosis, coccidiomycosis, schistosomiasis and malaria,

[and] or

(b) an immunogen selected from the group consisting of *Streptococcus, Staphylococcus, Neisseria, Escherichia coli, Shigella, Leishmania,* cytomegalovirus (CMV), respiratory syncytial virus, Epstein-Barr virus, herpes virus, parainfluenza virus, rotavirus, adenovirus, human immunodeficiency virus (HIV), hepatitis A virus, NonA NonB hepatitis virus, herpesvirus and flavivirus immunogens.

151 (amended). The kit of claim 43 in which at least one immunogen is [selected from the group consisting of]

(a) an immunogen of an organism which causes a disease selected from the group consisting of measles, mumps, rubella, diphtheria, pertussis, tetanus, anthrax, plague, encephalitis, meningitis, pneumonia, typhus, typhoid fever, Lyme disease, cholera, leprosy, influenza, varicella, rabies, dengue, toxoplasmosis, coccidiomycosis, schistosomiasis, and malaria, [and] or

(b) an immunogen selected from the group consisting of BCG, *Hemophilus influenza,* hepatitis B virus, polio virus, *Streptococcus, Staphylococcus, Neisseria, Escherichia coli, Shigella, Leishmania,* cytomegalovirus (CMV), respiratory syncytial virus, Epstein-Barr virus, herpes virus, parainfluenza virus, rotavirus, adenovirus, human immunodeficiency virus (HIV), hepatitis A virus, NonA/NonB hepatitis virus, and flavivirus immunogens.

152 (amended). The kit of claim 16 in which at least one immunogen is [selected from the group consisting of]

(a) an immunogen of an organism which causes a disease selected from the group consisting of measles, mumps, rubella, diphtheria, pertussis, tetanus, anthrax, plague, encephalitis, meningitis, pneumonia, [typhu] typhus, typhoid fever, Lyme disease, cholera, leprosy, influenza, varicella, rabies, dengue, toxoplasmosis, coccidiomycosis, schistosomiasis, and malaria,

[and] or

(b) an immunogen selected from the group consisting of BCG, *Hemophilus influenza*, hepatitis B virus, polio virus, *Streptococcus, Staphylococcus, Neisseria, Escherichia coli, Shigella, Leishmania*, cytomegalovirus (CMV), respiratory syncytial virus, Epstein-Barr virus, herpes virus, parainfluenza virus, rotavirus, adenovirus, human immunodeficiency virus (HIV), hepatitis A virus, NonA/NonB hepatitis virus, and flavivirus immunogens.